CLAIMS

What is claimed is:

1. A composition comprising the urokinase-type plasminogen activator (uPA) kringle in an amount effective to modulate one or more of the contractility and the angiogenic activity of a mammalian muscle or endothelial cell or tissue, wherein said uPA kringle shares at least about 75% homology with a polypeptide having the amino acid sequence corresponding to SEQ ID NO:1.

2. The composition of claim 1, further comprising one or more domains of uPA selected from the group consisting of the growth factor domain, the connecting peptide and the protease domain.

3. A composition comprising the growth factor domain of uPA in an amount effective to modulate the contractility of a mammalian muscle cell or tissue, wherein said growth factor domain shares at least about 75% homology with a polypeptide having the amino acid sequence corresponding to SEQ ID NO:2.

4. The composition of claim 3, further comprising one or more domains of uPA selected from the group consisting of the uPA kringle, the connecting peptide and the protease domain.

5. A composition comprising a polypeptide, said polypeptide (LMW-uPA) comprising the connecting peptide and protease domains of uPA in an amount effective to inhibit the contractility of a mammalian muscle cell or tissue, wherein said polypeptide shares at least about 75% homology with a polypeptide having the amino acid sequence corresponding to SEQ ID NO:5.

6. The composition of claim 1, wherein said cell is in a mammal.

7. The composition of claim 1, wherein said muscle cell is selected from the group consisting of a smooth muscle cell, a striated muscle cell and a cardiac muscle cell, and wherein said muscle tissue is selected from the group consisting of a smooth muscle tissue, a striated muscle tissue and a cardiac muscle tissue.

8. The composition of claim 1, further comprising an inducing compound in an amount effective to mediate the contraction of a mammalian muscle cell or tissue, wherein said inducing compound is selected from the group consisting of phenylepherine, epinepherine, acetylcholine and endothelin.

9. The composition of claim 2, comprising two chain urokinase (tcuPA), wherein said tcuPA shares at least about 75% homology with a polypeptide having the amino acid sequence corresponding to SEQ ID NO:3.

10. The composition of claim 4, comprising single chain urokinase (scuPA), wherein said scuPA shares at least about 75% homology with a polypeptide having the amino acid sequence corresponding to SEQ ID NO:3.

11. The composition of claim 2, comprising the amino terminal fragment (ATF) of uPA, wherein said ATF shares at least about 75% homology with a polypeptide having the amino acid sequence corresponding to SEQ ID NO:4.

12. The composition of claim 1, wherein said uPA kringle is an isolated kringle.

13. The composition of claim 3, wherein said growth factor domain is an isolated growth factor domain.

14. The composition of claim 11, wherein said ATF is an isolated ATF.

15. The composition of claim 1, wherein modulating the contractility of said muscle cell or tissue comprises enhancing or disinhibiting the contractility of said muscle cell or tissue.

16. The composition of claim 2, wherein modulating the contractility of said muscle cell or tissue comprises enhancing or disinhibiting the contractility of said muscle cell or tissue.

17. The composition of claim 1, wherein said cell or tissue is a vascular smooth muscle or endothelial cell or tissue, and further wherein said uPA kringle is present in an amount effective to modulate the angiogenic activity of said cell or tissue.

18. The composition of claim 2, wherein said cell or tissue is a vascular smooth muscle cell or tissue or a vascular endothelial cell or tissue.

19. The composition of claim 3, wherein modulating the contractility of said muscle cell or tissue comprises inhibiting the contractility of said muscle cell or tissue.

20. The composition of claim 4, wherein modulating the contractility of said muscle cell or tissue comprises inhibiting the contractility of said muscle cell or tissue.

21. The composition of claim 20, wherein said cell or tissue is a bronchial smooth muscle cell or tissue.

22. The composition of claim 2, comprising the deletion mutant polypeptide scuPA$^{\Delta 136\text{-}143}$ in an amount effective to enhance or disinhibit the contractility of a mammalian muscle cell or tissue, wherein said scuPA$^{\Delta 136\text{-}143}$ shares at

least about 75% homology with a polypeptide having the amino acid sequence corresponding to SEQ ID NO:6.

23. The composition of claim 4, comprising a deletion mutant polypeptide selected from the group consisting of Δkringle-scuPA and Δkringle-tcuPA in an amount effective to proteolytically activate plasminogen and to inhibit the contractility of a mammalian muscle cell or tissue, wherein said Δkringle-scuPA and said Δkringle-tcuPA each share at least about 75% homology with a polypeptide having the amino acid sequence corresponding to SEQ ID NO:7.

24. The composition of claim 2, wherein said composition comprises a polypeptide, said polypeptide comprising the amino terminal fragment (ATF) and the connecting peptide of uPA, wherein said polypeptide shares at least about 75% homology with a polypeptide having the amino acid sequence corresponding to SEQ ID NO:8.

25. The composition of claim 2, wherein said composition comprises a polypeptide, said polypeptide comprising the uPA kringle and the connecting peptide, wherein said polypeptide shares at least about 75% homology with a polypeptide having the amino acid sequence corresponding to SEQ ID NO:9.

26. The composition of claim 1, wherein said composition is in the form of a pharmaceutical composition.

27. The composition of claim 3, wherein said composition is in the form of a pharmaceutical composition.

28. A composition comprising one or more polypeptides, each of said polypeptides having an amino acid sequence selected from the group consisting of SEQ ID NO:1, SEQ ID NO:2, SEQ ID NO:3, SEQ ID NO:4, SEQ ID NO:5, SEQ ID

NO:6, SEQ ID NO:7, SEQ ID NO:8 and SEQ ID NO:9, wherein said one or more polypeptides are present in an amount effective to modulate one or more of the contractility and the angiogenic activity of a mammalian muscle or endothelial cell or tissue.

29. A composition comprising an isolated nucleic acid, said isolated nucleic acid having a nucleotide sequence which shares at least about 75% homology with a nucleotide sequence selected from the group consisting of SEQ ID NO:10, SEQ ID NO:11, SEQ ID NO:12, SEQ ID NO:13, SEQ ID NO:14, SEQ ID NO:15, SEQ ID NO:16, SEQ ID NO:17 and SEQ ID NO:18, wherein said isolated nucleic acid is present in said composition in an amount effective to transform a mammalian muscle or endothelial cell to provide transgene expression of a polypeptide at a level of expression effective to modulate one or more of the contractility and angiogenic activity of said muscle or endothelial cell after transfection with said isolated nucleic acid.

30. A method of treating a mammal afflicted with a disease or condition having as a symptom thereof one or more of abnormal muscle cell or tissue contractility and abnormal muscle or endothelial cell or tissue angiogenic activity, said method comprising

a) administering to the mammal a composition comprising the uPA kringle in an amount effective to modulate one or more of the contractility and the angiogenic activity of a mammalian muscle or endothelial cell or tissue, wherein said uPA kringle shares at least about 75% homology with a polypeptide having the amino acid sequence corresponding to SEQ ID NO:1; and

b) modulating one or more of the contractility and the angiogenic activity of said muscle or endothelial cell or tissue having one or more of abnormal contractility and abnormal angiogenic activity, whereby said disease or condition in the mammal is treated.

31. The method of claim 30, wherein said uPA kringle is a part of a polypeptide which shares at least about 75% homology with a polypeptide selected from the group consisting of SEQ ID NO:3 (tcuPA), SEQ ID NO:4 (ATF) and SEQ ID NO:6 (scuPA$^{\Delta 136\text{-}143}$), SEQ ID NO:8 and SEQ ID NO:9.

32. The method of claim 30, wherein said composition further comprises one or more of an agonist of the uPA kringle, an agonist of a binding protein of the uPA kringle, an antagonist of the uPA growth factor domain, an antagonist of the connecting peptide, an antagonist of a binding protein of the uPA growth factor domain, and an antagonist of a binding protein of the connecting peptide.

33. The method of claim 30, wherein said disease or condition is selected from the group consisting of hypotension, hypertension, atherosclerosis, stroke, heart attack, microvascular occlusions, thrombotic microangiopathies, surgically induced thrombotic disorders, angiogenic disorders, pulmonary fibrosis, asthma, tumor cell invasion, tumor cell angiogenesis, tumor cell metastasis, glaucoma diabetic retinopathy, a wound healing or clotting disorder, a uterine contraction disorder and male impotence.

34. A method for treating a mammal afflicted with a disease or condition having as a symptom thereof one or more of abnormal muscle cell or tissue contractility and abnormal muscle or endothelial cell or tissue angiogenic activity, said method comprising

a) administering to the mammal a composition comprising the uPA growth factor domain in an amount effective to modulate one or more of the contractility and the angiogenic activity of a mammalian muscle or endothelial cell or tissue, wherein said uPA growth factor domain shares at least about 75% homology with a polypeptide having the amino acid sequence corresponding to SEQ ID NO:2; and

b) modulating one or more of the contractility and the angiogenic activity of said muscle or endothelial cell or tissue having one or more of abnormal contractility and abnormal angiogenic activity, whereby the disease or condition in the mammal is treated.

35. The method of claim 34, wherein said composition comprises the uPA growth factor domain as part of a polypeptide which shares at least about 75% homology with a polypeptide having the amino acid sequence selected from the group consisting of SEQ ID NO:3 (scuPA), SEQ ID NO:4 (ATF), SEQ ID NO:6 ($scuPA^{\Delta 136-143}$), SEQ ID NO:7 (Δkringle-scuPA or Δkringle-tcuPA) and SEQ ID NO:8.

36. The method of claim 35, wherein said composition further comprises one or more of an agonist of the uPA growth factor domain, an agonist of the connecting peptide, an agonist of a binding protein of the growth factor domain, an agonist of a binding protein of the connecting peptide, an antagonist of the uPA kringle, and an antagonist of a binding protein of the uPA kringle.

37. The method of claim 35, wherein said composition is administered to said mammal in an amount effective to inhibit the contractility of a mammalian smooth muscle cell or tissue.

38. The method of claim 37, wherein said smooth muscle cell or tissue is a vascular smooth muscle cell or tissue, and wherein the disease or condition treated is hypertension.

39. The method of claim 30, wherein said disease or condition is a respiratory disease or condition selected from the group consisting of asthma, adult respiratory distress syndrome, primary pulmonary hypertension, microvascular thrombotic occlusion and a disorder associated with chronic intrapulmonary fibrin formation.

40. The method of claim 39, wherein said uPA kringle is present in an amount effective to inhibit the contractility of a bronchial smooth muscle cell or tissue and is a part of a polypeptide selected from the group consisting of an isolated kringle, ATF, tcuPA, scuPA$^{\Delta 136\text{-}143}$, SEQ ID NO:8 and SEQ ID NO:9.

41. The method of claim 30, wherein said disease or condition in the mammal sought to be treated has as a symptom thereof abnormally low vascular smooth muscle cell or tissue contractility.

42. The method of claim 41, wherein said uPA kringle is present in an amount effective to enhance or disinhibit the contractility of a vascular smooth muscle cell or tissue and is a part of a polypeptide selected from the group consisting of an isolated kringle, ATF, tcuPA, scuPA $^{\Delta 136\text{-}143}$, SEQ ID NO:8 and SEQ ID NO:9.

43. The method of claim 34, wherein said disease or condition has as a symptom thereof abnormally high vascular smooth muscle cell or tissue contractility.

44. The method of claim 43, wherein said uPA growth factor domain is present in said composition in an amount effective to inhibit the contractility of a vascular smooth muscle cell or tissue, and is present in said composition as a part of a polypeptide selected from the group consisting of an isolated growth factor domain, scuPA, Δkringle-scuPA and Δkringle-tcuPA.

45. A method of identifying a compound which is an agonist or antagonist of one or more of the uPA kringle or a binding protein thereof, the uPA growth factor domain or a binding protein thereof, and the connecting peptide or a binding protein thereof, upon the contractility or angiogenic activity of a mammalian muscle or endothelial cell or tissue, said method comprising

a) providing to a first cell and an otherwise identical second cell a composition comprising a polypeptide, said polypeptide comprising one or more of the uPA kringle, the uPA growth factor domain and the connecting peptide, wherein said polypeptide is present in said composition in an amount effective to modulate the contractility or angiogenic activity of a mammalian muscle or endothelial cell or tissue;

b) providing to said first cell a test compound;

c) assessing the contractility or the angiogenic activity of said first cell and said second cell prior to and after administering said composition and said test compound to said first cell, and prior to and after administering said composition to said second cell; and

d) comparing the contractility or angiogenic activity of said first cell with the contractility or angiogenic activity of said second cell prior to and after administration of said composition and said test compound, wherein, when the effect of said composition upon contractility or angiogenic activity in said first cell is either increased or decreased relative to the effect of said composition upon contractility or angiogenic activity in said second cell, a compound is identified which is an agonist or antagonist of one or more of the uPA kringle or a binding protein thereof, the uPA growth factor domain or a binding protein thereof, and the connecting peptide or a binding protein thereof, upon the contractility or angiogenic activity of a mammalian muscle or endothelial cell or tissue.

46. A method of treating a disease or condition in a mammal having as a symptom thereof one or more of abnormal muscle cell or tissue contractility and abnormal angiogenic activity, said method comprising

a) administering to the mammal an amount suspected to be effective for modulating the contractility or angiogenic activity of a mammalian muscle or endothelial cell or tissue of an agonist or antagonist of one or more of the uPA kringle or a binding protein thereof, the uPA growth factor domain or a binding protein thereof, and the connecting peptide or a binding protein thereof;

b) providing said agonist or antagonist to a muscle or endothelial cell or tissue in the mammal having abnormal contractility or abnormal angiogenic activity, or to a tissue or fluid which is contiguous therewith; and

c) modulating the effect of one or more of the uPA kringle or a binding protein thereof, the uPA growth factor domain or a binding protein thereof, and the connecting peptide or a binding protein thereof, upon said muscle or endothelial cell or tissue having abnormal contractility or abnormal angiogenic activity, whereby a disease or condition in the mammal having abnormal muscle cell or tissue contractility or abnormal angiogenic activity as a symptom thereof is treated.

47. The method of claim 46, wherein said disease or condition treated is the vascular disease hypertension.

48. The method of claim 47, wherein said agonist or antagonist is one or more of an antagonist to the uPA kringle, an antagonist to a binding protein of the uPA kringle, an agonist of the uPA growth factor domain, an agonist of a binding protein of the uPA growth factor domain, an agonist of the connecting peptide, and an agonist of a binding protein of the connecting peptide.

49. The method of claim 46, wherein said disease or condition treated is selected from the group consisting of asthma, adult respiratory distress syndrome, primary pulmonary hypertension, microvascular thrombotic occlusion and a disorder associated with chronic intrapulmonary fibrin formation.

50. The method of claim 49, wherein said agonist or antagonist is one or more of an agonist to the uPA kringle and an agonist to a binding protein of the uPA kringle.

51. A method of identifying whether a test protein is a binding protein of one or more of the uPA kringle, the uPA growth factor domain and the connecting peptide, said method comprising

a) assessing the contractility modulating effect or the angiogenic activity modulating effect of one or more of the uPA kringle, the uPA growth factor receptor and the connecting peptide upon a first cell or tissue, wherein said first cell or tissue comprises said test protein or is contiguous with a tissue or fluid of a mammal which comprises said test protein;

b) assessing the contractility modulating effect or the angiogenic activity modulating effect of one or more of said uPA kringle, said uPA growth factor receptor and said connecting peptide upon a second, otherwise identical cell or tissue which does not comprise said test protein and which is not contiguous with a tissue or fluid which comprises said test protein; and

c) comparing the contractility modulating effect or the angiogenic activity modulating effect in said first cell or tissue with the contractility modulating effect or the angiogenic activity modulating effect in said second cell or tissue, wherein, if the contractility modulating effect or the angiogenic activity modulating effect of one or more of said uPA kringle, said uPA growth factor receptor and said connecting peptide is greater in said first cell or tissue relative to said second cell or tissue, then said test protein is a binding protein of one or more of said uPA kringle, said uPA growth factor receptor and said connecting peptide.

52. A method of identifying a functional element of one or more of the uPA kringle, the uPA growth factor domain and the connecting peptide, said functional element participating in the modulation of contractility or angiogenic activity of a mammalian muscle or endothelial cell or tissue, said method comprising

a) preparing one or more mutant polypeptides which lack a portion of the amino acid sequence of one or more of the uPA kringle, the uPA growth factor domain and the connecting peptide;

b) assessing the ability of each of said mutant polypeptides to modulate the contractility or angiogenic activity of a mammalian muscle or endothelial cell or tissue once provided to said cell or tissue, or to a tissue or fluid which is contiguous with said cell or tissue;

c) identifying, from b) a mutant polypeptide which is not able to modulate the contractility or angiogenic activity of a mammalian muscle or endothelial cell or tissue; and

d) determining from c) and a) the corresponding deleted portion of the amino acid sequence of one or more of the uPA kringle, the uPA growth factor domain and the connecting peptide which participates in the modulation of muscle or endothelial cell or tissue contractility or angiogenic activity, whereby a functional element of one or more of the uPA kringle, the uPA growth factor domain and the connecting peptide is identified.

53. A method of treating a vascular disease or condition in a mammal having as a symptom thereof abnormally high fibrin clot formation, said method comprising

a) administering to said mammal a composition comprising one or more of Δkringle-scuPA, Δkringle-tcuPA, an antagonist of the uPA kringle and an antagonist of a binding protein of the uPA kringle in an amount effective to inhibit the contractility of a mammalian vascular smooth muscle cell or tissue, wherein said Δkringle-scuPA and Δkringle-tcuPA share at least about 75% homology with the polypeptide corresponding to SEQ ID NO:7;

b) providing said composition to an affected vascular smooth muscle cell or tissue of the cardiovascular system of the mammal which has or is prone to excessive fibrin clot formation, or to a tissue or fluid which is contiguous therewith; and

c) vasodilating said affected vascular smooth muscle cell or tissue by inhibiting the contractility of said affected vascular smooth muscle cell or tissue, thereby promoting both fibrin clot lysis and vasodilation in the affected area of the vasculature of the mammal, thereby treating said vascular disease or condition.

54. A kit for treating a disease or condition in a mammal, the disease or condition having as a symptom thereof one or more of abnormal muscle cell or tissue contractility and abnormal angiogenic activity, said kit comprising

a) a composition comprising a polypeptide, said polypeptide comprising one or more of the uPA kringle, the uPA growth factor domain, and the connecting peptide in an amount effective to modulate one or more of the contractility and the angiogenic activity of a mammalian muscle or endothelial cell or tissue; and

b) an instructional material.

55. The kit of claim 54, further comprising a sterile solvent suitable for dissolving or suspending said composition prior to administering said composition to said mammal.